12-18-06

AF/JFW

EXPRESS MAIL NO. EV 967485861 US DATE MAILED: December 15, 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Engleman, Edgar
Application No.	:	10/730,856
Filing Date	:	December 8, 2003
Title	:	COMBINATION THERAPY OF GAMMA-INTERFERON AND B-CELL SPECIFIC ANTIBODIES
Examiner	:	Ronald B. Schwadron
Group Art Unit	:	1644
Confirmation No.	:	3525
Attorney's Docket No.	:	03102.0013.PCUS01

APPEAL BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is an appeal of the Examiner's Final Rejection of pending Claims 1-8 submitted on or before the due date of December 17, 2006. Appellant hereby appeals from the Final Office Action mailed July 17, 2006.

1. REAL PARTY IN INTEREST

InterMune, Inc., the assignee of record, is the real party of interest in the application at the time this Brief is being filed.

2. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interference known to appellant, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

3. STATUS OF CLAIMS

Claims 1-8 are present in the application, have been rejected by the Examiner and are on appeal.

Claims 9-17 have been cancelled.

4. STATUS OF AMENDMENTS

No amendments have been filed subsequent to the Final Rejection.

5. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 is directed to a method of treating a B cell hyperproliferative disorder comprising administering to a patient gamma interferon at least 1 week prior to administering to said patient an effective dose of an antibody that specifically binds to an antigen present on said B cells. Claims 1 is supported by page 3, lines 7-9 and 17-19; page 4, lines 13-14; page 16, lines 22-23 and 28-33; and page 17, lines 1-2.

Claims 2-8 depend on Claim 1. Claim 2 recites that said B cell hyperproliferative disease is a Non-Hodgkin's lymphoma. Claim 2 is supported by page 10, lines 5-7 and page 14, line 26.

Claim 3 recites that said antibody is a monoclonal antibody. Claim 3 is supported by page 7, lines 30-32 and page 9, lines 1-4.

Claim 4 recites that said antibody is a humanized monoclonal antibody. Claim 4 is supported by page 9, lines 11-17.

Claim 5 recites that said antigen present on said B cells is CD20. Claim 5 is supported by page 8, lines 11-13 and 24-30.

Claim 6 recites that said antibody is administered at a dose of 0.001 to 30 mg/kg. Claim 6 is supported by page 17, lines 14-15.

Claim 7 recites that said gamma interferon is human gamma interferon. Claim 7 is supported by page 5, lines 3-4 and 10-12.

Claim 8 recites that said gamma interferon is administered at a dose of from 0.5 $\mu g/m^2$ to about 500 $\mu g/m^2$. Claim 8 is supported by page 17, lines 22-23.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether Claims 1-8 should be rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 6,455,043 to Grillo-Lopez in view of U.S. Patent No. 5,145,677 to Eichborn. In other words, is it obvious to administer IFN-γ at least 1 week prior to administering an antibody to a patient based on the disclosure that an anti-CD 20 antibody and a cytokine may be administered sequentially, in either order, to a patient?

7. ARGUMENTS

Rejection under 35 U.S.C. §103(a) as obvious over Grillo-Lopez in view of Eichborn

The §103(a) rejection of Claims 1-8 as being unpatentable over Grillo-Lopez in view of Eichborn should be reversed on the merits because the references cited, alone or in combination, do not teach or suggest administering IFN-γ at least 1 week prior to administering an antibody to a patient.

(a). Prior Art does not teach or suggest administering IFN-γ at least 1 week prior to administering an antibody to a patient.

Grillo-Lopez discloses that an "anti-CD20 antibody and the cytokine(s) may be administered sequentially, in either order, or in combination (col. 3, lines 35-36)", but fails to teach or suggest administering IFN-γ at least 1 week prior to administering an antibody to a patient. Examples cited by Grillo-Lopez vary significantly in time between cytokine administration and antibody administration: in Phase II studies of Rituximab®, an anti-CD20 antibody, with GM-CSF, patients were administered GM-CSF starting one hour prior to Rituximab® (col. 15, lines 50-52); in Phase I and Phase II studies of Rituximab® with G-CSF, patients were administered G-CSF starting two days prior to administration of Rituximab® (col. 13, lines 54-55); and in a combination trial of Rituximab® plus interferon alpha, patients were administered interferon alpha five weeks prior to administration of Rituximab® (col. 13, lines 31-33). Cytokines are a diverse group of small secreted proteins which mediate immunological, inflammatory and infectious responses. GM-CSF is produced by macrophages and stimulates stem cells to produce granulocytes and macrophages. G-CSF is a glycoprotein produced by endothelium, macrophages and various immune cells to stimulate the survival, proliferation, differentiation and function of neturophil granulocyte progenitor cells and mature neturophils. Interferon alpha is a Type I interferon secreted by leukocytes and stimulates both macrophage and natural killer cells. Unlike any of the cytokines mentioned by Grillo-Lopez, interferon gamma is a Type II interferon released by Th1 cells and recruits leukocytes to a site of infection resulting in increased inflammation. A person of ordinary skill in the art would not have a reasonable expectation of success in reasonably determining the optimal time difference between administration of gamma interferon, one particular cytokine, and administration of an anti-B cell

antibody without undue experimentation based merely upon the broad and generalized disclosure by Grillo-Lopez of completely different cytokines. In *Metabolite Laboratories Inc. v. Laboratory Corporation of America Holdings* (370 F.3d 1354, 71 USPQ2d 1081 (Fed. Cir. 2004)), the Federal Circuit found that such prior art references disclosing a broad genus did not inherently disclose all species within that broad category. Thus, the reference by Grillo-Lopez disclosing a broad genus of cytokines does not inherently disclose the Applicant's particular species, gamma interferon. Furthermore, in *Minnesota Mining & Manufacturing Co. v. Johnson & Johnson Orthopaedics, Inc.* (976 F.2d 1559, 24 USPQ2d 1321 (Fed. Cir. 1992)), the Federal Circuit found that such broad and generalized disclosures by prior art references were meaningless and provided no guidance.

(b). Administering IFN-γ at least 1 week prior to administering an antibody to a patient provides unexpected advantages.

By administering gamma interferon at least 1 week prior to the antibody administration, the immunomodulatory activity of the IFN-gamma is initiated prior to the antibody treatment (pg. 17, lines 3-5). In addition, both gamma interferon and the antibody, Rituximab, have difficult side effects. Gamma interferon produces flu-like side effects (increased body temperature, fatigue, headache, muscle pain, convulsion, dizziness), hair thinning and depression. Rituximab produces side effects including black and tarry stools, bleeding gums, bloating, blood in the urine and stools, burred vision, cough, dizziness, pain or tenderness around eyes and cheekbones and troubled breathing. Introducing gamma interferon at least one week before Rituximab allows for better tolerability and greater adherence to the antibody treatment by minimizing the side effects that would occur without initiating the patient to gamma interferon before administering anti-B cell antibodies. Instead of a patient coping with side effects from the administration of two new drugs, the patient has a chance to tolerate the first drug—gamma interferon—for at least 1 week before the additional administration of a second drug—the anti-B cell antibodies.

At best, Grillo-Lopez describes the genus of cytokine and anti-B-cell antibody combination therapy, but with no guidance on how to determine the optimal time difference

between cytokine and anti-B cell administration, this disclosure of the genus does not render obvious Applicant's particular species invention—interferon gamma administration at least 1 week prior to administration of anti-B cell antibodies. Accordingly, Applicant respectfully submits that the critical feature of the presently claimed invention—administering interferon gamma at least 1 week prior to administration of the antibody—has not been taught or suggested by Grillo-Lopez. Eichborn only discloses the use of gamma for treatment of lymphoma at a dosage encompassed by that recited in claim 8. Therefore, the addition of Eichborn does not correct this deficiency.

8. CLAIM APPENDIX

A Claim Appendix, containing a copy of the claims involved in the appeal, is attached herewith.

9. CONCLUSION

For the reasons stated above, the Examiner's rejection of Claims 1-8 is erroneous. The Honorable Board is respectfully requested to reverse the Examiner's rejection of all claims on appeal and remand the application to the Examiner for allowance. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, including fees under §1.17 to deposit account 08-3038, reference Attorney Docket No. 03102.0013.PCUS01.

Respectfully submitted,

Dated: December 15, 2006

By: \Carolyn Tang\
Registration No. 57,881

Correspondence Address:

HOWREY LLP
1950 University Avenue, 4th Floor
East Palo Alto, CA 94303
Telephone: (650) 798-3570

CLAIM APPENDIX

1. A method of treating a B cell hyperproliferative disorder, the method comprising: administering to a patient IFN-γ (gamma interferon) at least 1 week prior to administering to said patient an effective dose of an antibody that specifically binds to an antigen present on said B cells.

2. The method according to claim 1, wherein said B cell hyperproliferative disease in a Non-Hodgkin's lymphoma.

3. The method according to claim 1, wherein said antibody is a monoclonal antibody.

4. The method according to claim 1, wherein said antibody is a humanized monoclonal antibody.

5. The method according to claim 1, wherein said antigen present on said B cells is CD20.

6. The method according to claim 1, wherein said antibody is administered at a dose of 0.001 to 30 mg/kg.

7. The method according to claim 1, wherein said IFN-γ is human IFN-γ.

8. The method according to claim 1, wherein said IFN-γ is administered at a dose of from 0.5 μg/m2 to about 500 μg/m2.

PTO/SB/17 (07-06)
Approved for use through 01/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL for FY 2006

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($)250

Complete If Known	
Application Number	10/730,856
Filing Date	December 8, 2003
First Named Inventor	Edgar ENGLEMAN
Examiner Name	Ronald B. SCHWADRON
Art Unit	1644
Attorney Docket No.	03102.0013.PCUS01

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 08-3038 Deposit Account Name: Howrey LLP

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below
☐ Charge fee(s) indicated below, **except for the filing fee**
☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17
☒ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION (All the fees below are due upon filing or may be subject to a surcharge.)

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims		Extra Claims	Fee ($)		Fees Paid ($)
_____	- 20 or HP =	_____	x _____	=	_____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims		Extra Claims	Fee ($)		Fees Paid ($)
_____	- 3 or HP =	_____	x _____	=	_____

HP = highest number of independent claims paid for, if greater than 3

Multiple Dependent Claims Fee ($)	Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee ($)		Fee Paid ($)
_____	- 100 =	_____	/50=	_____	(round **up** to a whole number) x	_____	=	_____

4. OTHER FEE(S)

	Fee Paid ($)
Non-English Specification, $130 fee (no small entity discount)	_____
Other (e.g., late filing surcharge): Appeal Brief under 37 CFR § 1.27(a)	250

SUBMITTED BY

Signature		Registration No. 41,131 (Attorney/Agent)	Telephone (650) 798-3570
Name (Print/Type)	Viola T. Kung		Date December 15, 2006